=> file reg
FILE 'REGISTRY' ENTERED AT 14:24:13 ON 01 APR 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8
DICTIONARY FILE UPDATES: 31 MAR 2003 HIGHEST RN 501072-24-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

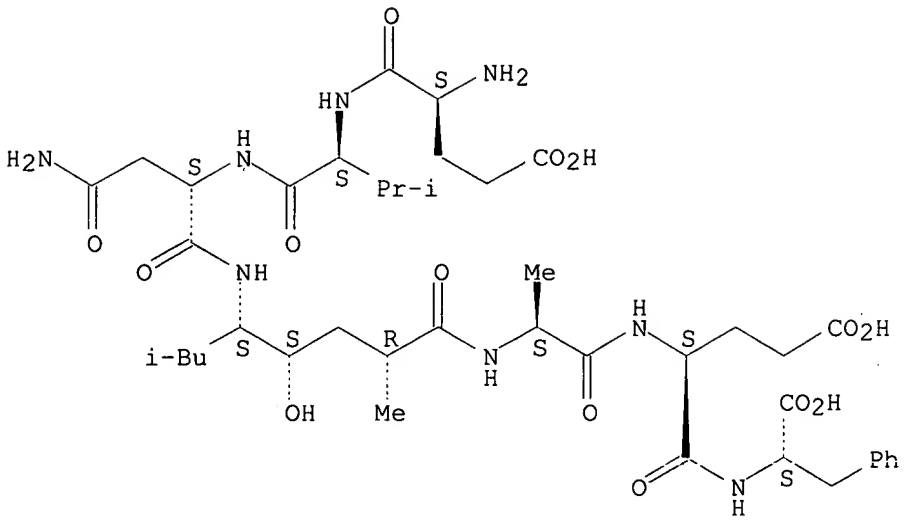
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d l5

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **314266-76-7** REGISTRY
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN OM 99-2
FS PROTEIN SEQUENCE; STEREOSEARCH
DR 313355-78-1
MF **C41 H64 N8 O14**
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, TOXCENTER, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.



9 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> file caplus
FILE 'CAPLUS' ENTERED AT 14:25:11 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 1 Apr 2003 VOL 138 ISS 14
FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file caplus; d que 18
FILE 'CAPLUS' ENTERED AT 14:32:53 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December

FILE COVERS 1907 - 1 Apr 2003 VOL 138 ISS 14
FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)
L5 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C41H64N8O14/MF
L6 8 SEA FILE=CAPLUS ABB=ON PLU=ON L5
L7 118341 SEA FILE=CAPLUS ABB=ON PLU=ON ?ALZHEIMER? OR ?DEMENTIA? OR ?MEMOR?
L8 6 SEA FILE=CAPLUS ABB=ON PLU=ON L6 AND L7

=> file uspatful; d que l11
FILE 'USPATFULL' ENTERED AT 14:33:15 ON 01 APR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 1 Apr 2003 (20030401/PD)
FILE LAST UPDATED: 1 Apr 2003 (20030401/ED)
HIGHEST GRANTED PATENT NUMBER: US6543053
HIGHEST APPLICATION PUBLICATION NUMBER: US2003061649
CA INDEXING IS CURRENT THROUGH 1 Apr 2003 (20030401/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 1 Apr 2003 (20030401/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

```
>>> USPATFULL and USPAT2 can be accessed and searched together          <<<
>>> through the new cluster USPATALL.  Type FILE USPATALL to           <<<
>>> enter this cluster.                                                <<<
>>>                                                                    <<<
>>> Use USPATALL when searching terms such as patent assignees,        <<<
>>> classifications, or claims, that may potentially change from      <<<
>>> the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  (314266-76-7/BI OR 105018-81-
                 3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR
                 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6
                 /BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR
                 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-
                 9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR
                 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04
                 -8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR
                 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84
                 -2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR
                 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91
                 -1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR
                 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI
                  OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/
                 BI)
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C41H64N8O14/MF
L9             4 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L10       496190 SEA FILE=USPATFULL ABB=ON  PLU=ON  ?ALZHEIMER? OR ?DEMENTIA?
                 OR ?MEMOR?
L11            3 SEA FILE=USPATFULL ABB=ON  PLU=ON  L9 AND L10

=> dup rem l8 l11
FILE 'CAPLUS' ENTERED AT 14:33:24 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 14:33:24 ON 01 APR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L8
PROCESSING COMPLETED FOR L11
L13            9 DUP REM L8 L11 (0 DUPLICATES REMOVED)
                 ANSWERS '1-6' FROM FILE CAPLUS
                 ANSWERS '7-9' FROM FILE USPATFULL

=> d ibib abs hitstr l13 1-9

L13  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:153949  CAPLUS
DOCUMENT NUMBER:          136:305914
TITLE:                    Substrate and inhibitor profile of BACE
                          (.beta.-secretase) and comparison with other mammalian
                          aspartic proteases
AUTHOR(S):                Gruninger-Leitch, Fiona; Schlatter, Daniel; Kung,
                          Erich; Nelbock, Peter; Dobeli, Heinz
CORPORATE SOURCE:         CNS Research, Hoffmann-La Roche Ltd, Basel, CH-4070,
                          Switz.
```

SOURCE: Journal of Biological Chemistry (2002), 277(7), 4687-4693
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

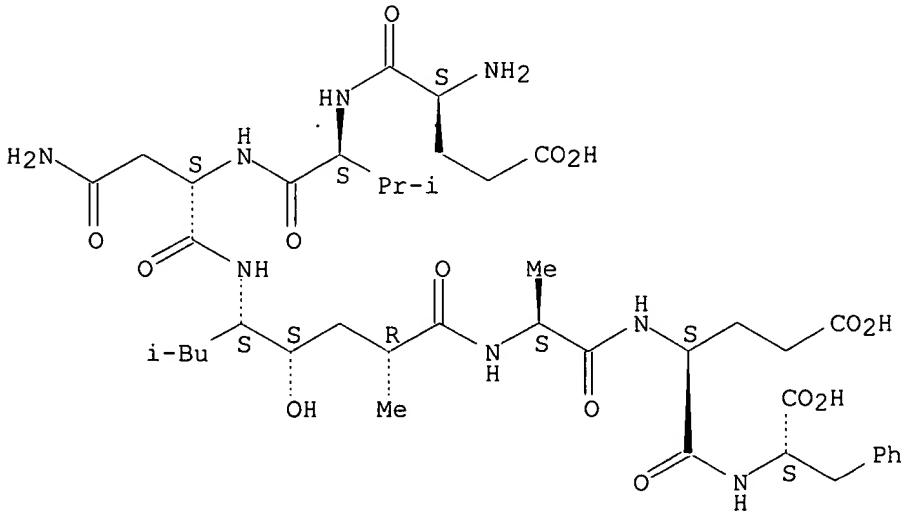
AB The full-length and ectodomain forms of .beta.-site APP cleavage enzyme (BACE) have been cloned, expressed in Sf9 cells, and purified to homogeneity. This aspartic protease cleaves the amyloid precursor protein at the .beta.-secretase site, a crit. step in the **Alzheimer**'s disease pathogenesis. Comparison of BACE to other aspartic proteases such as cathepsin D and E, napsin A, pepsin, and renin revealed little similarity with respect to the substrate preference and inhibitor profile. On the other hand, these parameters are all very similar for the homologous enzyme BACE2. Based on a collection of decameric substrates, it was found that BACE has a loose substrate specificity and that the substrate recognition site in BACE extends over several amino acids. In common with the aspartic proteases mentioned above, BACE prefers a leucine residue at position P1. Unlike cathepsin D etc., BACE accepts polar or acidic residues at positions P2' and P1 but prefers bulky hydrophobic residues at position P3. BACE displays poor kinetic consts. toward its known substrates (wild-type substrate, SEVKM .dwnarw. DAEFR, Km = 7 .mu.M, Kcat = 0.002 s-1; Swedish mutant, SEVNL .dwnarw. DAEFR, Km = 9 .mu.M, Kcat = 0.02 s-1). A new substrate (VVEVDA .dwnarw. AVTP, Km = 1 .mu.M, Kcat = 0.004) was identified by serendipity.

IT **314266-76-7**, OM99-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrate and inhibitor profile of BACE .beta.-secretase and comparison with other mammalian aspartic proteases)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

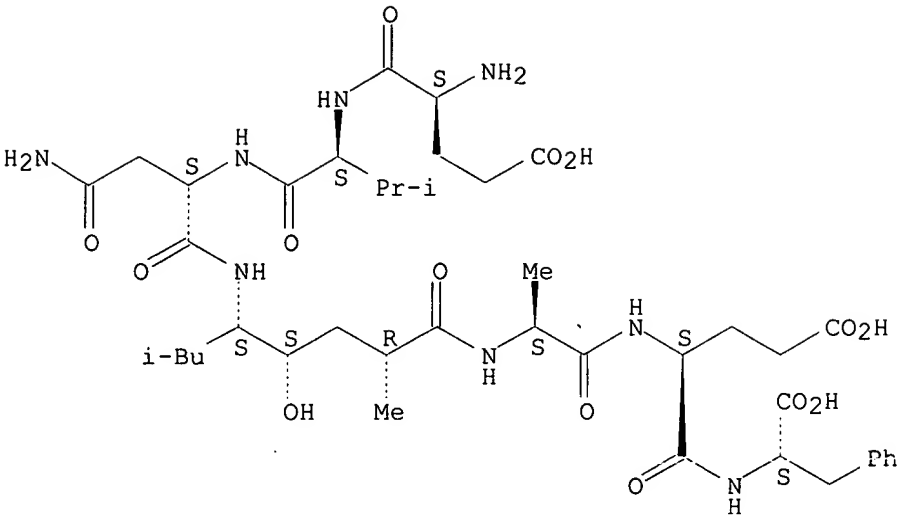
L13 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:728546 CAPLUS
DOCUMENT NUMBER: 138:85411
TITLE: Recombinant insect cell expression and purification of human .beta.-secretase (BACE-1) for X-ray crystallography
AUTHOR(S): Bruinzeel, Wouter; Yon, Jeff; Giovannelli, Silvio; Masure, Stefan
CORPORATE SOURCE: Department of Assay Development & HTS, Johnson & Johnson Pharmaceutical Research & Development, Beerse, B-2340, Belg.
SOURCE: Protein Expression and Purification (2002), 26(1), 139-148
CODEN: PEXPEJ; ISSN: 1046-5928
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human .beta.-secretase (BACE-1) is a type I integral membrane aspartic protease that catalyzes the internal cleavage of the amyloid precursor protein (APP), generating the N-terminus of the A.beta. peptide. The generation and subsequent extracellular deposition of A.beta.1-42 peptide into amyloid plaques in the brain constitute one of the hallmarks of **Alzheimer**'s disease (AD), a common debilitating neurodegenerative disorder. Inhibition of BACE-1 is considered an excellent therapeutic strategy against AD. To generate pure enzyme for protein crystallog. and subsequent structure-based drug design, we have expressed a sol., unglycosylated, 6.times.His-tagged form of proBACE-1 in insect cells using baculovirus infection. To avoid prodn. of a mixt. of the pro-enzyme form and the mature form of BACE-1, the proprotein convertase furin was coexpressed with proBACE-1, leading to almost complete proteolytic activation of the recombinant enzyme. The mature enzyme was secreted in the conditioned medium of BACE-1/furin coinfected HighFive insect cells. Secreted BACE-1 protein was purified to homogeneity from the medium using subsequent Ni-chelate affinity chromatog., anion-exchange chromatog., hydrophobic interaction chromatog., and gel filtration. To avoid autoproteolysis, all purifn. steps were performed at pH values outside the activity range of BACE-1. The purified, biol. active enzyme was homogeneous on SDS/PAGE and had the expected sequence and mol. mass detd. by N-terminal amino acid sequencing and mass spectrometry, resp. Moreover, the prepn. showed a single peak of the expected size with only 17% polydispersity using dynamic light scattering anal. The yield of BACE-1 from fermn. cultures was approx. 0.1 mg pure enzyme per L of cell culture medium. The purified protein was successfully used to generate BACE-1/inhibitor co-crystals and to det. the crystal structure of the complex by X-ray anal. The availability of substantial quantities of active, homogeneous enzyme will be of great help in future structure-based drug design efforts in the search for efficient protease inhibitor drugs to treat AD.

IT **314266-76-7**, OM 99-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(recombinant insect cell expression and purifn. of human .beta.-secretase (BACE-1))

RN 314266-76-7 CAPLUS
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1194449	A2	20020410	EP 2000-943236	20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.: US 1999-141363P P 19990628

US 1999-168060P P 19991130
US 2000-177836P P 20000125
US 2000-178368P P 20000127
US 2000-210292P P 20000608
US 2000-603713 A3 20000627
US 2000-604608 A3 20000627
WO 2000-US17742 W 20000627

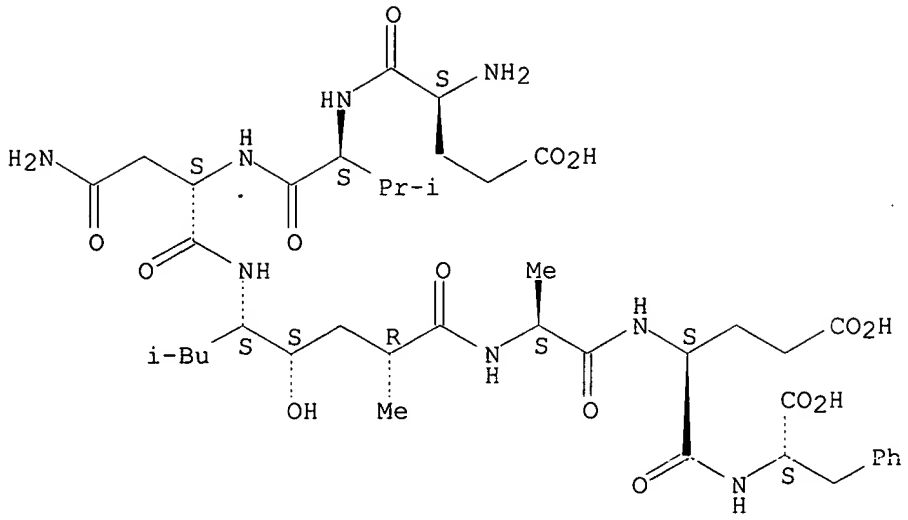
AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer**'s disease.

IT **314266-76-7P**, OM 99-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of memapsin 2 and use thereof)

RN 314266-76-7 CAPLUS

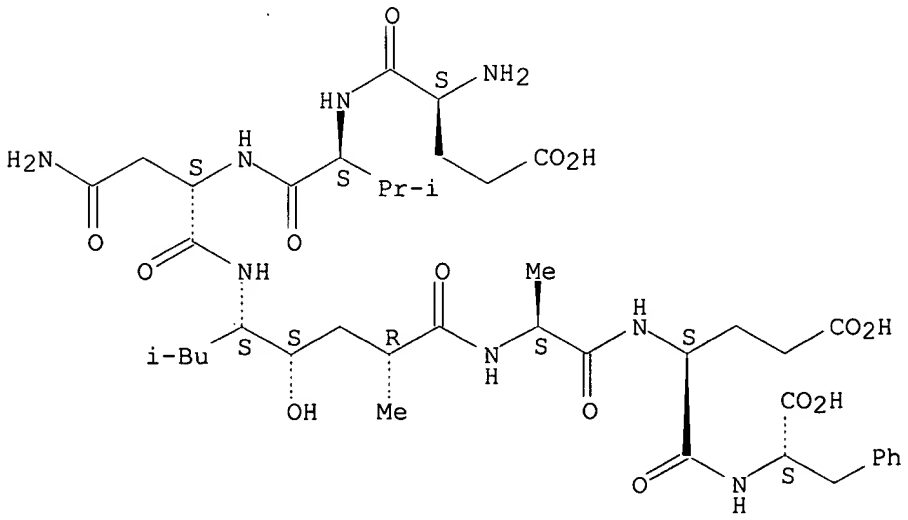
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **314266-76-7**
RL: PRP (Properties)
(unclaimed sequence; inhibitors of memapsin 2 and use thereof)
RN 314266-76-7 CAPLUS
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12487 CAPLUS
DOCUMENT NUMBER: 134:68049
TITLE: Catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for **Alzheimer**'s disease treatment

INVENTOR(S): Tang, Jordan J. N.; Lin, Xinli; Koelsch, Gerald
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000663	A2	20010104	WO 2000-US17661	20000627
WO 2001000663	A3	20011004		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1196609	A2	20020417	EP 2000-943208	20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003503072	T2	20030128	JP 2001-507069	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.:

US 1999-141363P	P	19990628
US 1999-168060P	P	19991130
US 2000-177836P	P	20000125
US 2000-178368P	P	20000127
US 2000-210292P	P	20000608
US 2000-603713	A3	20000627
US 2000-604608	A3	20000627
WO 2000-US17661	W	20000627

AB A method for producing catalytically active recombinant memapsin 2 comprising expression in a bacteria and refolding the recombinant memapsin 2 under conditions which dissoc. and then slowly refold the enzyme into a catalytically active form is disclosed. A method of isolating inhibitors of cleavage by memapsin 2 comprising adding to one or more potential inhibitors of catalytically active recombinant memapsin 2 , and a substrate for memapsin 2, and screening for decreased cleavage of the substrate by the inhibitors, wherein the inhibitors are in a library of small synthetic mols., like proteins and peptides. Alternatively, the inhibitors are oligonucleotides preventing or decreasing expression of catalytically active memapsin 2. A method for designing or obtaining inhibitors of catalytically active memapsin 2 comprising modeling an inhibitor based on the crystn. coordinates of memapsin 2 or parameters. A database comprising binding properties and chem. structures of compds. designed or screened by modeling an inhibitor based on the crystn. coordinates of memapsin 2 or parameters is claimed. A method of treating or preventing **Alzheimer**'s disease comprising administering to a patient in need thereof an inhibitor of memapsin 2 which binds to the active site of the memapsin 2 defined by the presence of two catalytic aspartic residues and substrate binding cleft, is also claimed. The cDNAs of two new human membrane-assocd. aspartic proteases, memapsin 1 and memapsin 2, have been cloned and sequenced. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate

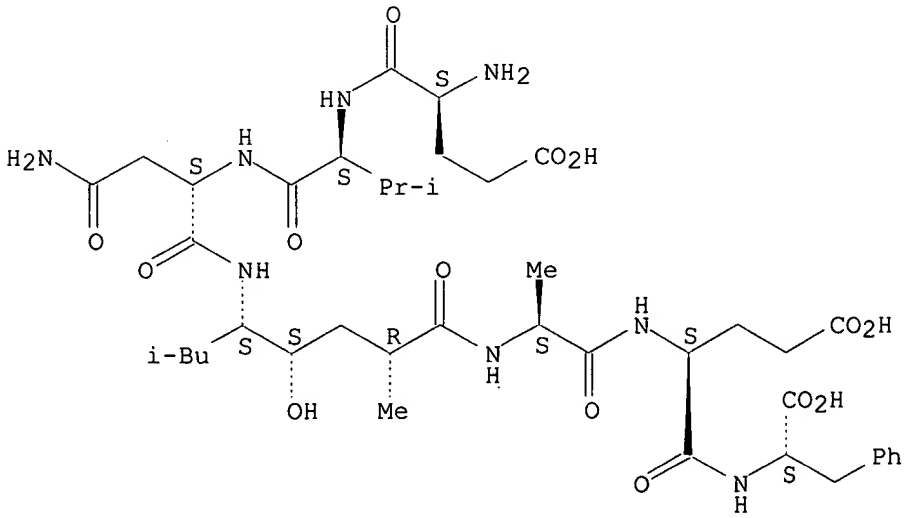
analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Fig. 1). The inhibition const. of OM99-2 is 1.6 x 109 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer**'s disease.

IT **314266-76-7DP**, OM 99-2, complexes with memapsin 2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for **Alzheimer**'s disease treatment)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. .



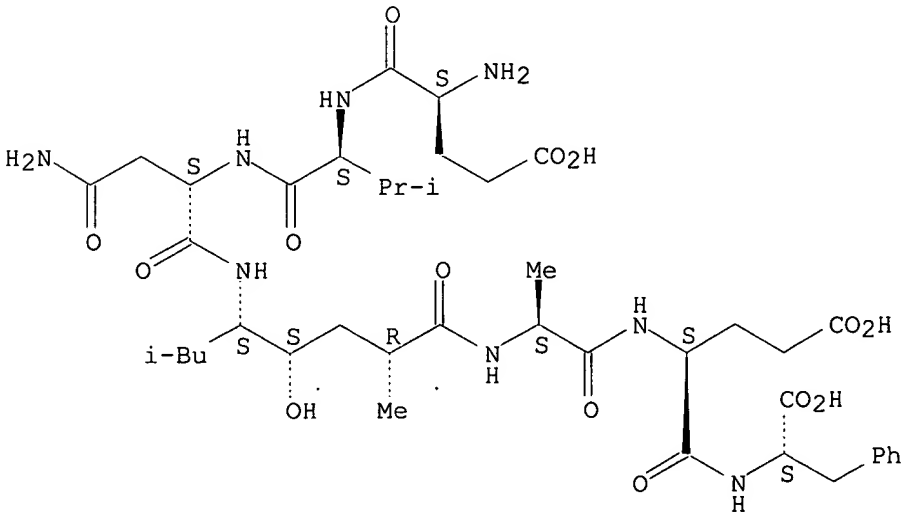
L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:558376 CAPLUS
DOCUMENT NUMBER: 135:282682
TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar;

Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch, Gerald; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, 60607, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(18), 2865-2868
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the .beta.-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the progression of **Alzheimer**'s disease. On the basis of the X-ray crystal structure of our lead inhibitor (2, OM99-2 with eight residues) bound to memapsin, we have reduced the mol. wt. and designed potent memapsin inhibitors. Structure-based design and preliminary structure-activity studies have been presented.

IT **314266-76-7**, OM 99-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-based design of memapsin 2 inhibitors for the treatment of **Alzheimer**'s disease)

RN 314266-76-7 CAPLUS
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:724245 CAPLUS
DOCUMENT NUMBER: 134:53089
TITLE: Structure of the protease domain of memapsin 2 (.beta.-secretase) complexed with inhibitor
AUTHOR(S): Hong, Lin; Koelsch, Gerald; Lin, Xinli; Wu, Shili;

Terzyan, Simon; Ghosh, Arun K.; Zhang, Xuenjun C.; Tang, Jordan

CORPORATE SOURCE: Protein Studies Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104, USA

SOURCE: Science (Washington, D. C.) (2000), 290(5489), 150-153
CODEN: SCIEAS; ISSN: 0036-8075

PUBLISHER: American Association for the Advancement of Science

DOCUMENT TYPE: Journal

LANGUAGE: English

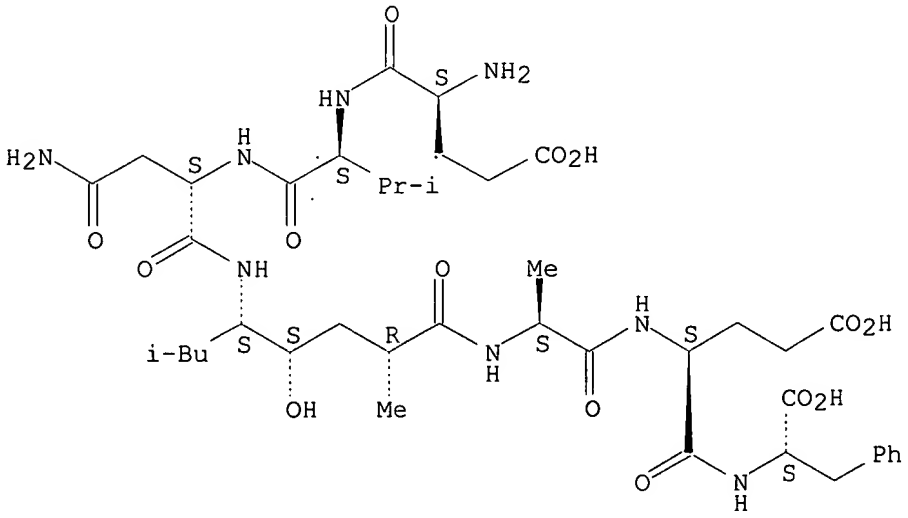
AB Memapsin 2 (.beta.-secretase) is a membrane-assocd. aspartic protease involved in the prodn. of .beta.-amyloid peptide in **Alzheimer**'s disease and is a major target for drug design. We detd. the crystal structure of the protease domain of human memapsin 2 complexed to an eight-residue inhibitor at 1.9 angstrom resoln. The active site of memapsin 2 is more open and less hydrophobic than that of other human aspartic proteases. The subsite locations from S4 to S2' are well defined. A kink of the inhibitor chain at P2' and the change of chain direction of P3' and P4' may be mimicked to provide inhibitor selectivity.

IT **314266-76-7D**, OM 99-2, complexes with memapsin 2
RL: PRP (Properties)
(structure of the protease domain of memapsin 2 (.beta.-secretase) complexed with inhibitor)

RN 314266-76-7 CAPLUS

CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 9 USPATFULL

ACCESSION NUMBER: 2002:294717 USPATFULL

TITLE: Catalytically active recombinant memapsin and methods of use thereof

INVENTOR(S): Lin, Xinli, Edmond, OK, UNITED STATES
Koelsch, Gerald, Oklahoma City, OK, UNITED STATES
Tang, Jordan J.N., Edmond, OK, UNITED STATES

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164760	A1	20021107
APPLICATION INFO.:	US 2001-795903	A1	20010228 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-604608, filed on 27 Jun 2000, PENDING

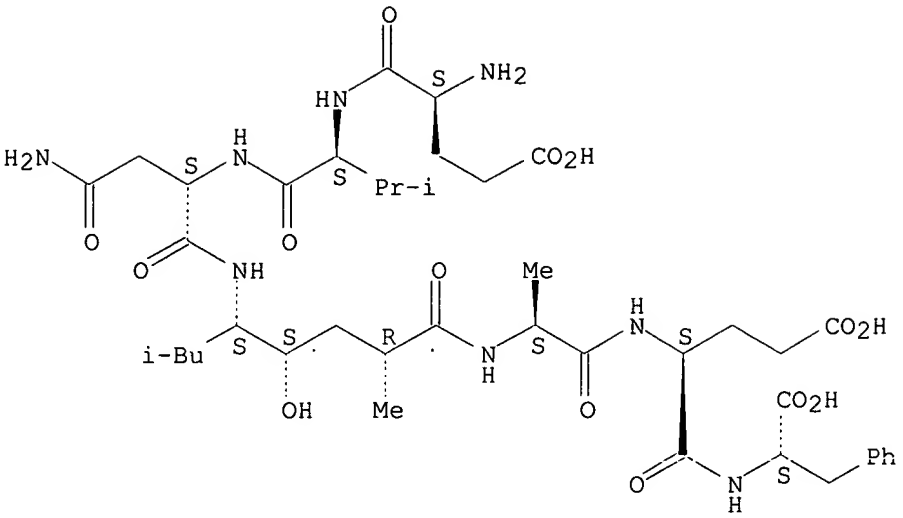
	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-141363P	19990628 (60)
	US 1999-168060P	19991130 (60)
	US 2000-177836P	20000125 (60)
	US 2000-178368P	20000127 (60)
	US 2000-210292P	20000608 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogues including isosteres at the sites of the critical amino acid residues were developed and the substrate analogues, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer**'s disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **314266-76-7DP**, OM 99-2, complexes with memapsin 2
(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)
RN 314266-76-7 USPATFULL
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 8 OF 9 USPATFULL

ACCESSION NUMBER:	2002:214213 USPATFULL
TITLE:	Inhibitors of memapsin 2 and use thereof
INVENTOR(S):	Koelsch, Gerald, Oklahoma City, OK, UNITED STATES Tang, Jordan J.N., Edmond, OK, UNITED STATES Hong, Lin, Oklahoma City, OK, UNITED STATES Ghosh, Arun K., River Forest, IL, UNITED STATES
PATENT ASSIGNEE(S):	Oklahoma Medical Research Foundation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002115600	A1	20020822
APPLICATION INFO.:	US 2001-845226	A1	20010430 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-603713, filed on 27 Jun 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-141363P	19990628 (60)
	US 1999-168060P	19991130 (60)
	US 2000-177836P	20000125 (60)
	US 2000-178368P	20000127 (60)
	US 2000-210292P	20000608 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Patrea L. Pabst, Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA, 30309-3450
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	12 Drawing Page(s)
LINE COUNT:	2377

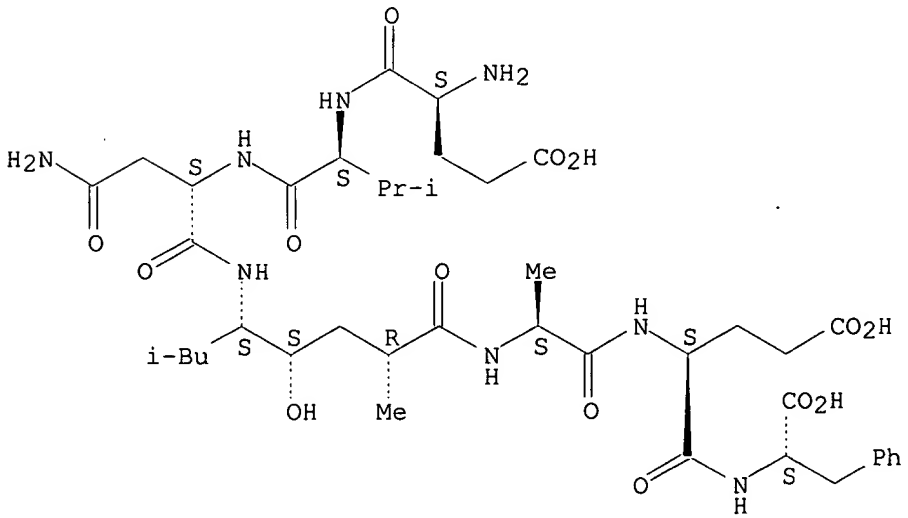
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit

the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogues including isosteres at the sites of the critical amino acid residues were developed and the substrate analogues, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the tliree dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer**'s disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **314266-76-7DP**, OM 99-2, complexes with memapsin 2
(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)
RN 314266-76-7 USPATFULL
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 9 OF 9 USPATFULL
ACCESSION NUMBER: 2002:92777 USPATFULL
TITLE: Catalytically active recombinant memapsin and methods of use thereof
INVENTOR(S): Tang, Jordan J. N., Edmond, OK, UNITED STATES
Lin, Xinli, Edmond, OK, UNITED STATES
Koelsch, Gerald, Oklahoma City, OK, UNITED STATES

Hong, Lin, Oklahoma City, OK, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002049303	A1	20020425
APPLICATION INFO.:	US 2001-796264	A1	20010228 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-604608, filed on 27 Jun 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-141363P	19990628 (60)
	US 1999-168060P	19991130 (60)
	US 2000-177836P	20000125 (60)
	US 2000-178368P	20000127 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATREA L. PABST, HOLLAND & KNIGHT LLP, SUITE 2000, ONE ATLANTIC CENTER, 1201 WEST PEACHTREE STREET, N.E., ATLANTA, GA, 30309-3400
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2441

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the critical amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (FIG. 1). The inhibition constant of OM99-2 is 1.6.times.10.sup.-9 M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of **Alzheimer**'s disease.

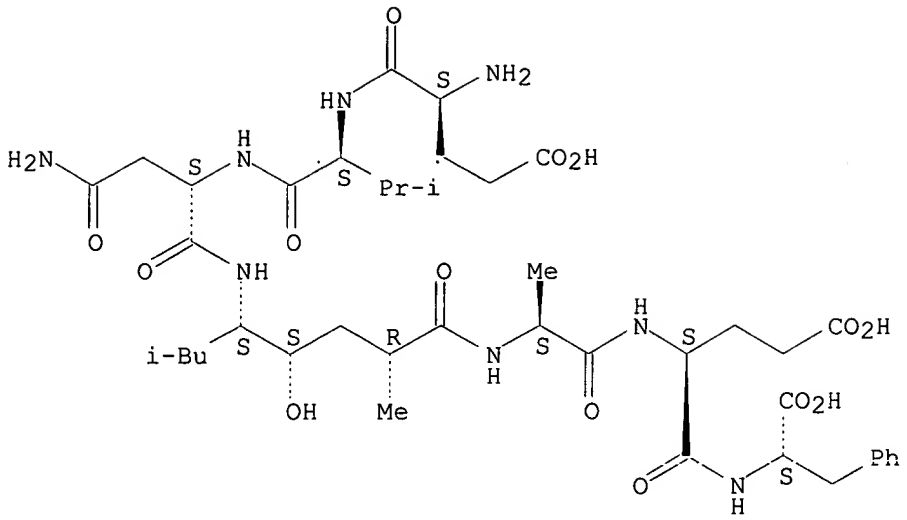
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **314266-76-7DP**, OM 99-2, complexes with memapsin 2
(catalytically active recombinant memapsin 2, 3D crystal structure based inhibitor design, synthesis, and screening, for Alzheimer's disease treatment)

RN 314266-76-7 USPATFULL

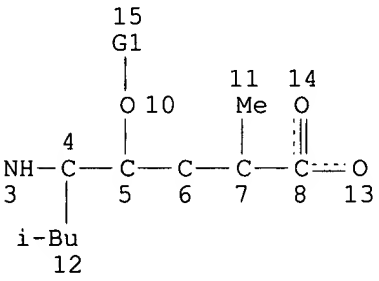
CN L-Phenylalanine, L-.alpha.-glutamyl-L-valyl-L-asparaginyl-(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyloctanoyl-L-alanyl-L-.alpha.-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> file home
FILE 'HOME' ENTERED AT 14:35:14 ON 01 APR 2003

```
=> file reg; d stat que l30
FILE 'REGISTRY' ENTERED AT 17:40:46 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   31 MAR 2003  HIGHEST RN 501072-24-8
DICTIONARY FILE UPDATES:  31 MAR 2003  HIGHEST RN 501072-24-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L28                 STR
```



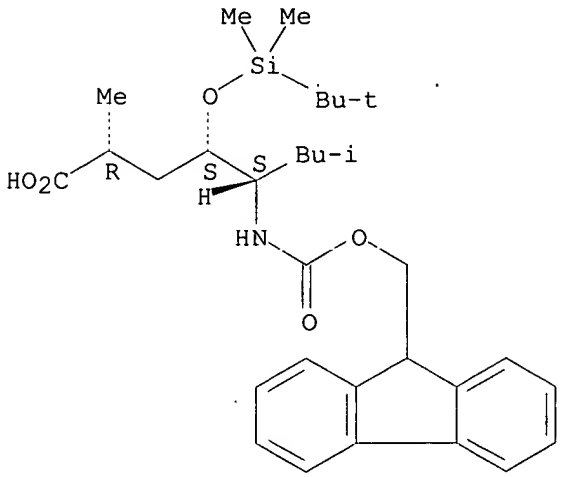
Note: This structure was searched to cover the compounds of 37e and 40a, whose structures were not included in the CAS reference of the inventors' work.

Please note: Structures 1-4 retrieved in the full file search do not match the structures of 37e and 40a. So these compounds are not present in CAS + could not be searched as products or reactants

```
VAR G1=H/SI
NODE ATTRIBUTES:
CONNECT IS E1  RC AT  13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  12

STEREO ATTRIBUTES: NONE
L30             4 SEA FILE=REGISTRY SSS FUL L28

100.0% PROCESSED 121547 ITERATIONS                    4 ANSWERS
SEARCH TIME: 00.00.02


=> d 130 1-4

L30  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2003 ACS
RN   271601-66-2  REGISTRY
CN   Octanoic acid, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[(9H-fluoren-9-
```

ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H45 N O5 Si
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

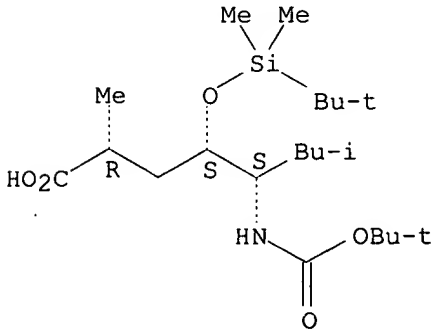


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 271601-65-1 REGISTRY
CN Octanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H43 N O5 Si
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

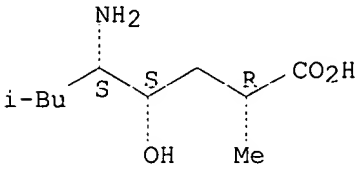


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1962 TO DATE)
4 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 91464-94-7 REGISTRY
CN Octanoic acid, 5-amino-4-hydroxy-2,7-dimethyl-, [2R-(2R*,4S*,5S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H21 N O3
LC STN Files: CA, CAPLUS

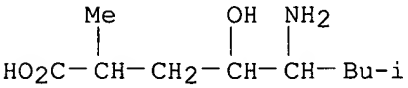
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L30 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 89028-17-1 REGISTRY
CN Octanoic acid, 5-amino-4-hydroxy-2,7-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C10 H21 N O3
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> file caplus; d que l31
FILE 'CAPLUS' ENTERED AT 17:41:22 ON 01 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Apr 2003 VOL 138 ISS 14
FILE LAST UPDATED: 31 Mar 2003 (20030331/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)

L16 2 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C16H27NO5/MF

L31 3 SEA FILE=CAPLUS ABB=ON PLU=ON L16/P

Note: L31 = compound in claim 37a as a product

=> d ibib abs hitstr l31 1-3

L31 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1194449	A2	20020410	EP 2000-943236	20000627
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:

US 1999-141363P P 19990628
US 1999-168060P P 19991130
US 2000-177836P P 20000125
US 2000-178368P P 20000127
US 2000-210292P P 20000608
US 2000-603713 A3 20000627
US 2000-604608 A3 20000627
WO 2000-US17742 W 20000627

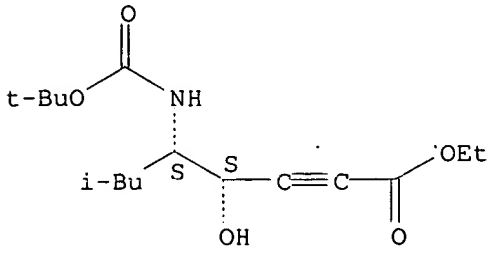
AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **105018-82-4P 105018-89-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of memapsin 2 and use thereof)

RN 105018-82-4 CAPLUS

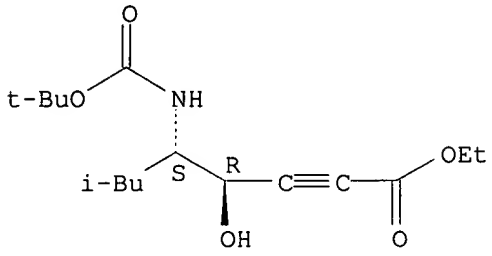
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



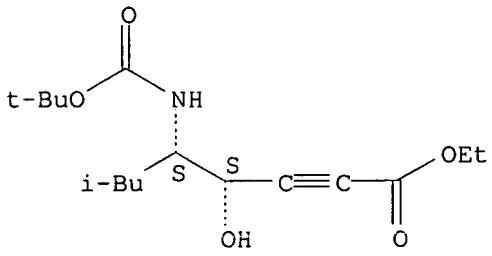
RN 105018-89-1 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L31 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:188678 CAPLUS
DOCUMENT NUMBER: 133:12663
TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA
SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.
IT **105018-82-4P 105018-89-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and activity of potent inhibitors for human brain memapsin 2 (.beta.-secretase))
RN 105018-82-4 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

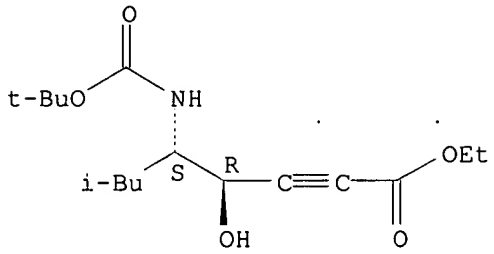
Absolute stereochemistry.



RN 105018-89-1 CAPLUS

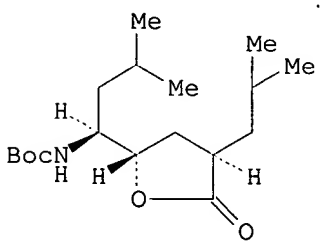
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

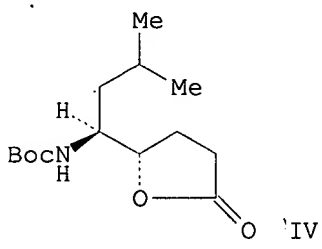


REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

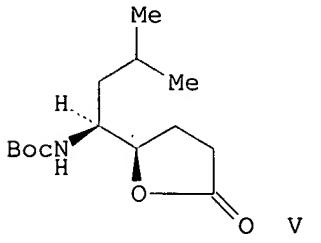
L31 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:627255 CAPLUS
DOCUMENT NUMBER: 105:227255
TITLE: A short, stereoselective synthesis of the lactone precursor to 2R,4S,5S hydroxyethylene dipeptide isosteres
AUTHOR(S): Fray, Andrew H.; Kaye, Robert L.; Kleinman, Edward F.
CORPORATE SOURCE: Dep. Med. Chem., Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Journal of Organic Chemistry (1986), 51(25), 4828-33
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 105:227255
GI



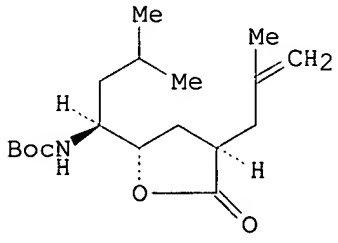
I



IV



V



VI

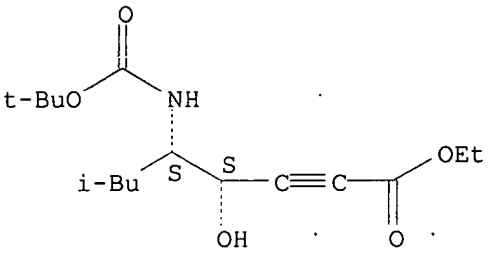
AB Lactone I (Boc = Me3CO2C), a precursor to the 2R,4S,5S hydroxyethylene dipeptide isostere unit, was synthesized stereoselectively in 4 steps from N-Boc-L-leucinal (II) in 13% overall yield. Addn. of LiC.tplbond.CCO2Et to II gave Me2CHCH2CH(NHBoc)CH(OH)C.tplbond.CCO2Et (III) as a mixt. of the (4S,5S)- and (4R,5S)-diastereomers. Redn. of the acetylenic function of

III and subsequent lactonization gave a readily separable 4.5:1 mixt. of acetones IV and V. Direct alkylation of IV with methallyl bromide and lithium hexamethyldisilazide as base yielded lactone VI, which was catalytically reduced to I. The structure of VI was confirmed by x-ray anal. Peptides contg. hydroxyethylene dipeptide isosteres with the above chirality are potent inhibitors of aspartyl proteases.

IT **105018-82-4P 105018-89-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrogenation-lactonization of)

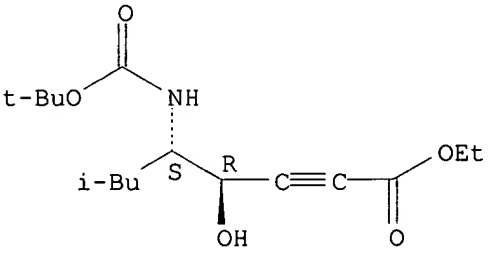
RN 105018-82-4 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 105018-89-1 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d que 140
L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/

```
                BI)
L16             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C16H27NO5/MF
L17             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C14H25NO4/MF
L40             3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L17/P AND L16 (L) (RCT OR
                RACT)/RL
```

Note: L40 = compound of claim 37c as a product

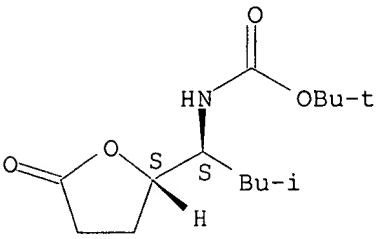
```
=> d ibib abs hitstr l40 1-3

L40  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2001:12489  CAPLUS
DOCUMENT NUMBER:          134:80832
TITLE:                    Inhibitors of memapsin 2 and use thereof
INVENTOR(S):              Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S):       Oklahoma Medical Research Foundation, USA; The Board
                          of Trustees of the University of Illinois
SOURCE:                   PCT Int. Appl., 86 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2001000665      A2   20010104      WO 2000-US17742  20000627
     WO 2001000665      A3   20010927
     WO 2001000665      C2   20020725
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     EP 1194449         A2   20020410      EP 2000-943236   20000627
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     JP 2003506322      T2   20030218      JP 2001-507071   20000627
     US 2002049303      A1   20020425      US 2001-796264   20010228
     US 2002164760      A1   20021107      US 2001-795903   20010228
     US 2002115600      A1   20020822      US 2001-845226   20010430
PRIORITY APPLN. INFO.:                  US 1999-141363P  P  19990628
                                        US 1999-168060P  P  19991130
                                        US 2000-177836P  P  20000125
                                        US 2000-178368P  P  20000127
                                        US 2000-210292P  P  20000608
                                        US 2000-603713   A3 20000627
                                        US 2000-604608   A3 20000627
                                        WO 2000-US17742  W  20000627
AB   Methods for the prodn. of purified, catalytically active, recombinant
     memapsin 2 have been developed.  The substrate and subsite specificity of
     the catalytically active enzyme have been detd.  The substrate and subsite
     specificity information was used to design substrate analogs of the
     natural memapsin 2 substrate that can inhibit the function of memapsin 2.
     The substrate analogs are based on peptide sequences, shown to be related
     to the natural peptide substrates for memapsin 2.  The substrate analogs
     contain at least one analog of an amide bond which is not capable of being
     cleaved by memapsin 2.  Processes for the synthesis of two substrate
```

analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **105018-81-3P 105018-82-4P 105018-83-5P**
105018-89-1P
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(inhibitors of memapsin 2 and use thereof)

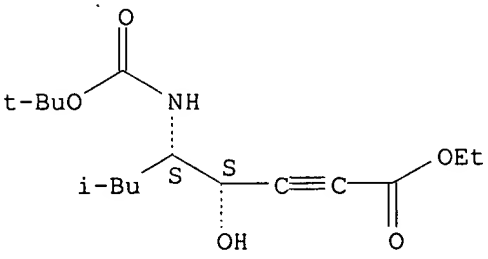
RN 105018-81-3 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



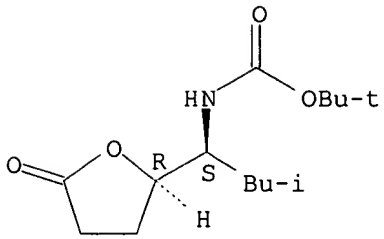
RN 105018-82-4 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



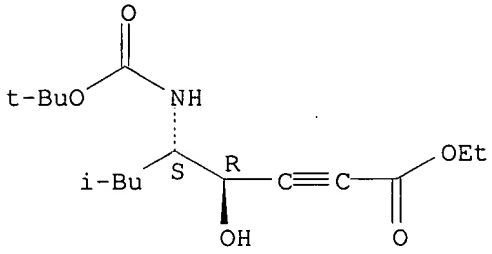
RN 105018-83-5 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



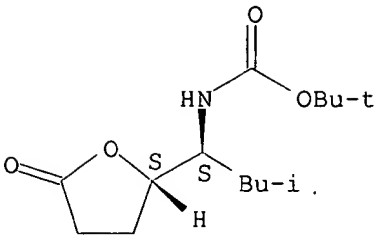
RN 105018-89-1 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



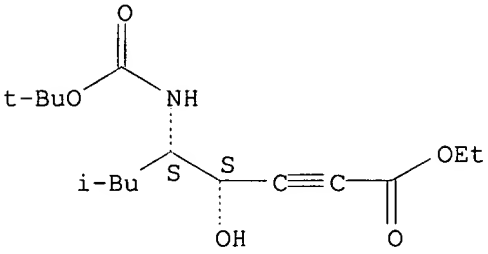
L40 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:188678 CAPLUS
DOCUMENT NUMBER: 133:12663
TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA
SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.
IT **105018-81-3P 105018-82-4P 105018-83-5P 105018-89-1P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(prepn. and activity of potent inhibitors for human brain memapsin 2 (.beta.-secretase))
RN 105018-81-3 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



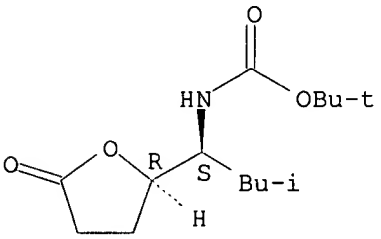
RN 105018-82-4 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



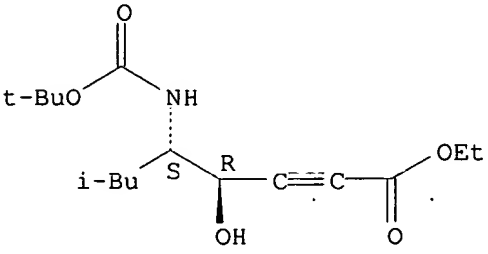
RN 105018-83-5 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



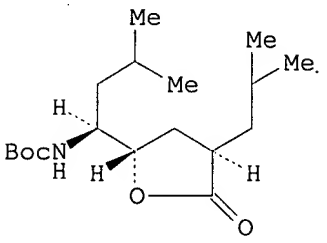
RN 105018-89-1 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

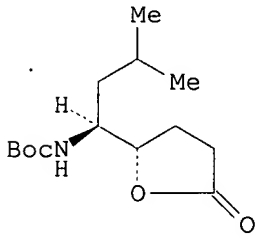


REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

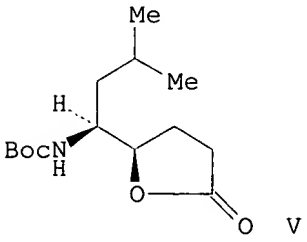
L40 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1986:627255 CAPLUS
DOCUMENT NUMBER: 105:227255
TITLE: A short, stereoselective synthesis of the lactone precursor to 2R,4S,5S hydroxyethylene dipeptide isosteres
AUTHOR(S): Fray, Andrew H.; Kaye, Robert L.; Kleinman, Edward F.
CORPORATE SOURCE: Dep. Med. Chem., Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Journal of Organic Chemistry (1986), 51(25), 4828-33
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 105:227255
GI



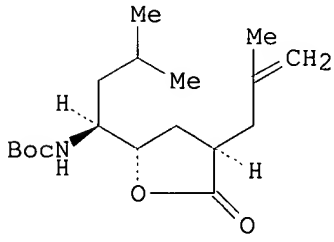
I



IV



V



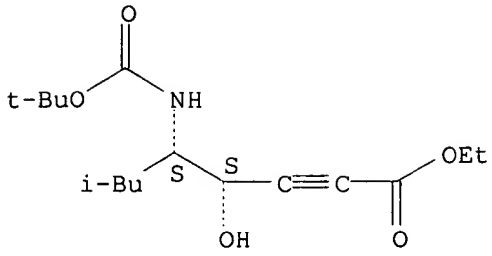
VI

AB Lactone I (Boc = Me3CO2C), a precursor to the 2R,4S,5S hydroxyethylene dipeptide isostere unit, was synthesized stereoselectively in 4 steps from N-Boc-L-leucinal (II) in 13% overall yield. Addn. of LiC.tplbond.CCO2Et to II gave Me2CHCH2CH(NHBoc)CH(OH)C.tplbond.CCO2Et (III) as a mixt. of the (4S,5S)- and (4R,5S)-diastereomers. Redn. of the acetylenic function of III and subsequent lactonization gave a readily separable 4.5:1 mixt. of acetones IV and V. Direct alkylation of IV with methallyl bromide and lithium hexamethyldisilazide as base yielded lactone VI, which was catalytically reduced to I. The structure of VI was confirmed by x-ray anal. Peptides contg. hydroxyethylene dipeptide isosteres with the above chirality are potent inhibitors of aspartyl proteases.

IT **105018-82-4P 105018-89-1P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(prepn. and hydrogenation-lactonization of)

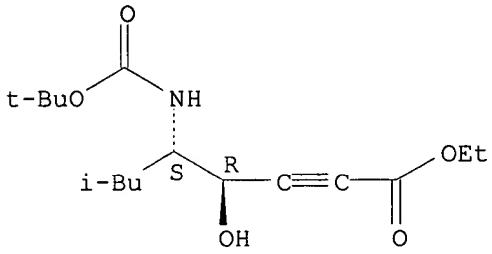
RN 105018-82-4 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



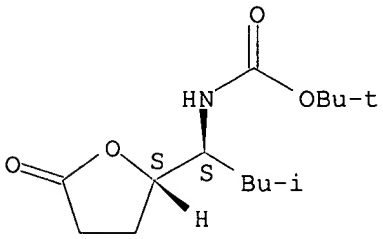
RN 105018-89-1 CAPLUS
CN 2-Octynoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-7-methyl-, ethyl ester, (4R,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



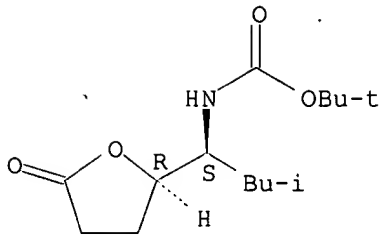
IT **105018-81-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and stereoselective alkylation of, with methallyl bromide)
RN 105018-81-3 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2S)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **105018-83-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 105018-83-5 CAPLUS
CN Carbamic acid, [(1S)-3-methyl-1-[(2R)-tetrahydro-5-oxo-2-furanyl]butyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.




```
=> d que l41
L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  (314266-76-7/BI OR 105018-81-
                 3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR
                 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6
                 /BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR
                 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-
                 9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR
                 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04
                 -8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR
                 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84
                 -2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR
                 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91
                 -1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR
                 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI
                  OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/
                 BI)
L17            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C14H25NO4/MF
L18            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C15H27NO4/MF
L41            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L18/P AND L17 (L) (RCT OR
                 RACT)/RL
```

Note: L41 = compound of 37d as a product

```
=> d ibib abs l41 1-4

L41  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:521789  CAPLUS
DOCUMENT NUMBER:          137:90187
TITLE:                    Inhibitors of memapsin 2 and their use in Alzheimer's
                          disease treatment
INVENTOR(S):              Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.
PATENT ASSIGNEE(S):       Oklahoma Medical Research Foundation, USA; The Board
                          of Trustees of the University of Illinois
SOURCE:                   PCT Int. Appl., 74 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE          APPLICATION NO.  DATE
     ----------------    ----  --------      ---------------  --------
     WO 2002053594        A2   20020711      WO 2001-US50826  20011228
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
```

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-258705P P 20001228
US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which dets. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of 1.4-61.4 x 109 M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

L41 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:558376 CAPLUS
DOCUMENT NUMBER: 135:282682
TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar; Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch, Gerald; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, 60607, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(18), 2865-2868
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the .beta.-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the progression of Alzheimer's disease. On the basis of the X-ray crystal structure of our lead inhibitor (2, OM99-2 with eight residues) bound to memapsin, we have reduced the mol. wt. and designed potent memapsin inhibitors. Structure-based design and preliminary structure-activity studies have been presented.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof

INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1194449	A2	20020410	EP 2000-943236	20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.:

US 1999-141363P	P	19990628
US 1999-168060P	P	19991130
US 2000-177836P	P	20000125
US 2000-178368P	P	20000127
US 2000-210292P	P	20000608
US 2000-603713	A3	20000627 ✓
US 2000-604608	A3	20000627
WO 2000-US17742	W	20000627

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's

disease.

L41 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:188678 CAPLUS
DOCUMENT NUMBER: 133:12663
TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA
SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que l44
L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)
L20 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C13H26N2O4/MF
L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C11H21NO4/MF
L44 2 SEA FILE=CAPLUS ABB=ON PLU=ON L21/P AND L20 (L) (RCT OR RACT)/RL

note: L44 = compounds of 38b as a product combined with 38a as a reactant

=> d ibib abs l44 1-2

L44 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:521789 CAPLUS
DOCUMENT NUMBER: 137:90187
TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's disease treatment
INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053594	A2	20020711	WO 2001-US50826	20011228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258705P P 20001228
US 2001-275756P P 20010314

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which dets. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of 1.4-61.4 x 109 M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

L44 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1194449	A2	20020410	EP 2000-943236	20000627
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.:

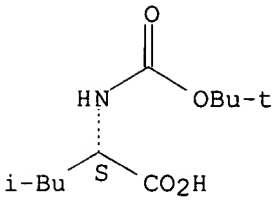
US 1999-141363P	P	19990628
US 1999-168060P	P	19991130
US 2000-177836P	P	20000125
US 2000-178368P	P	20000127
US 2000-210292P	P	20000608
US 2000-603713	A3	20000627
US 2000-604608	A3	20000627
WO 2000-US17742	W	20000627

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

=> d hitstr l44 1-4

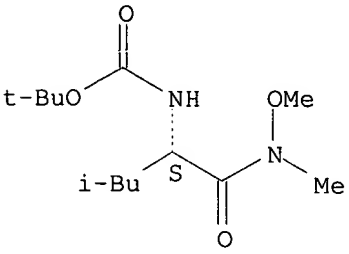
L44 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
IT **13139-15-6P 87694-50-6P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(inhibitors of memapsin 2 and their use in Alzheimer's disease treatment)
RN 13139-15-6 CAPLUS
CN L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



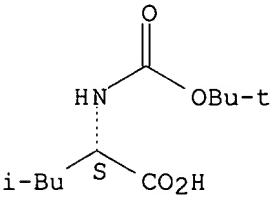
RN 87694-50-6 CAPLUS
CN Carbamic acid, [(1S)-1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



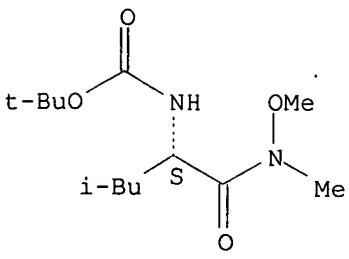
L44 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
IT **13139-15-6P 87694-50-6P**
RL: **RCT (Reactant)**; SPN (Synthetic preparation); PREP (Preparation); **RACT (Reactant or reagent)**
(inhibitors of memapsin 2 and use thereof)
RN 13139-15-6 CAPLUS
CN L-Leucine, N-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 87694-50-6 CAPLUS
CN Carbamic acid, [(1S)-1-[(methoxymethylamino)carbonyl]-3-methylbutyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



```
=> d que l36
L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  (314266-76-7/BI OR 105018-81-
                 3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR
                 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6
                 /BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR
                 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-
                 9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR
                 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04
                 -8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR
                 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84
                 -2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR
                 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91
                 -1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR
                 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI
                  OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/
                 BI).
L22            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L4 AND C21H43NO5SI/MF
L36            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L22/P
```

Note: L36 = compounds of claim 39 as a product

```
=> d ibib abs hitstr l36 1-4

L36  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:521789  CAPLUS
DOCUMENT NUMBER:          137:90187
TITLE:                    Inhibitors of memapsin 2 and their use in Alzheimer's
                          disease treatment
INVENTOR(S):              Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.
PATENT ASSIGNEE(S):       Oklahoma Medical Research Foundation, USA; The Board
                          of Trustees of the University of Illinois
SOURCE:                   PCT Int. Appl., 74 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2002053594      A2   20020711      WO 2001-US50826  20011228
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
```

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258705P P 20001228
US 2001-275756P P 20010314

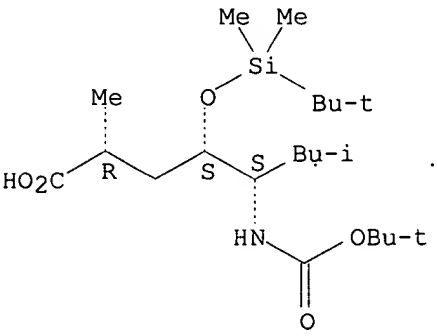
AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which dets. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of 1.4-61.4 x 109 M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **271601-65-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of memapsin 2 and their use in Alzheimer's disease treatment)

RN 271601-65-1 CAPLUS

CN Octanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L36 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:558376 CAPLUS

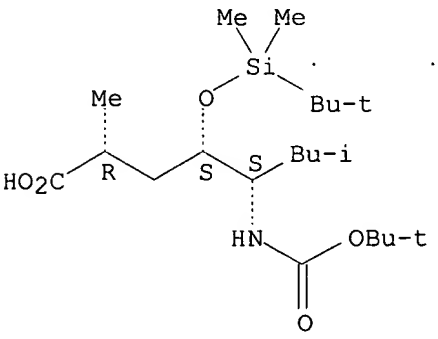
DOCUMENT NUMBER: 135:282682

TITLE: Structure-based design: potent inhibitors of human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Bilcer, Geoffrey; Harwood, Cynthia; Kawahama, Reiko; Shin, Dongwoo; Hussain, Khaja Azhar; Hong, Lin; Loy, Jeffrey A.; Nguyen, Chan; Koelsch,

Gerald; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, 60607, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(18), 2865-2868
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Memapsin 2 (.beta.-secretase) is one of two proteases that cleave the .beta.-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-.beta. peptide (A.beta.) in the human brain, a key event in the progression of Alzheimer's disease. On the basis of the X-ray crystal structure of our lead inhibitor (2, OM99-2 with eight residues) bound to memapsin, we have reduced the mol. wt. and designed potent memapsin inhibitors. Structure-based design and preliminary structure-activity studies have been presented.
IT **271601-65-1P**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(structure-based design of memapsin 2 inhibitors for the treatment of Alzheimer's disease)
RN 271601-65-1 CAPLUS
CN Octanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1194449	A2	20020410	EP 2000-943236	20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.:		
US 1999-141363P	P	19990628
US 1999-168060P	P	19991130
US 2000-177836P	P	20000125
US 2000-178368P	P	20000127
US 2000-210292P	P	20000608
US 2000-603713	A3	20000627
US 2000-604608	A3	20000627
WO 2000-US17742	W	20000627

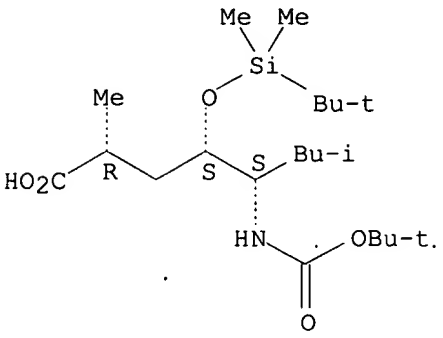
AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **271601-65-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of memapsin 2 and use thereof)

RN 271601-65-1 CAPLUS

CN Octanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



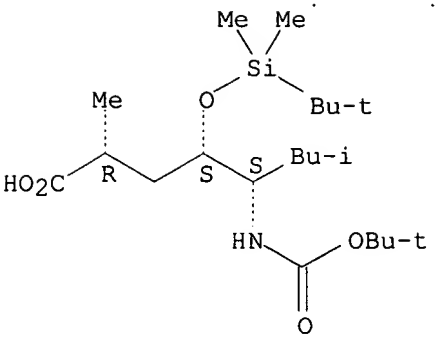
L36 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:188678 CAPLUS
DOCUMENT NUMBER: 133:12663
TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)
AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan
CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA
SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.

IT **271601-65-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and activity of potent inhibitors for human brain memapsin 2 (.beta.-secretase))

RN 271601-65-1 CAPLUS
CN Octanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que l37
L4 48 SEA FILE=REGISTRY ABB=ON PLU=ON (314266-76-7/BI OR 105018-81-3/BI OR 105018-82-4/BI OR 105018-83-5/BI OR 105018-89-1/BI OR 13139-15-6/BI OR 158736-49-3/BI OR 169057-47-0/BI OR 18162-48-6/BI OR 186142-28-9/BI OR 217895-20-0/BI OR 217895-23-3/BI OR 24424-99-5/BI OR 252256-37-4/BI OR 265641-18-7/BI OR 271601-63-9/BI OR 271601-65-1/BI OR 271601-66-2/BI OR 315675-00-4/BI OR 315675-01-5/BI OR 315675-02-6/BI OR 315675-03-7/BI OR 315675-04-8/BI OR 315675-05-9/BI OR 315675-06-0/BI OR 315675-07-1/BI OR 315675-08-2/BI OR 315675-09-3/BI OR 315726-83-1/BI OR 315726-84-2/BI OR 315726-85-3/BI OR 315726-86-4/BI OR 315726-87-5/BI OR 315726-88-6/BI OR 315726-89-7/BI OR 315726-90-0/BI OR 315726-91-1/BI OR 315726-92-2/BI OR 315726-93-3/BI OR 315726-94-4/BI OR 316146-76-6/BI OR 316146-77-7/BI OR 58521-45-2/BI OR 61-90-5/BI OR 623-47-2/BI OR 6638-79-5/BI OR 86167-59-1/BI OR 87694-50-6/BI)
L24 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C31H45NO5SI/MF
L37 3 SEA FILE=CAPLUS ABB=ON PLU=ON L24/P

Note: L37 = compounds of claim 40 B as a product

=> d ibib abs hitstr l37 1-3

L37 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:521789 CAPLUS
DOCUMENT NUMBER: 137:90187
TITLE: Inhibitors of memapsin 2 and their use in Alzheimer's disease treatment
INVENTOR(S): Tang, Jordan J. N.; Koelsch, Gerald; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053594	A2	20020711	WO 2001-US50826	20011228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258705P P 20001228
US 2001-275756P P 20010314

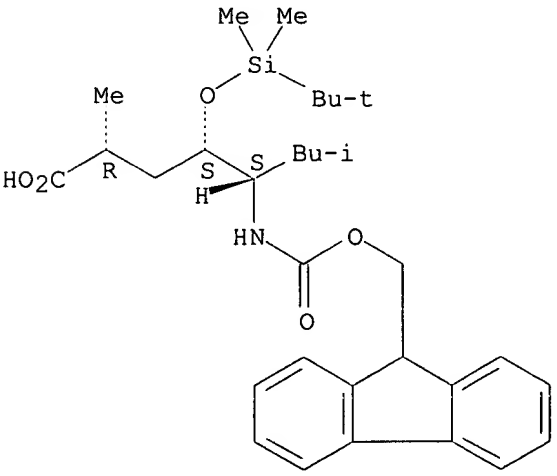
AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. by a method which dets. the initial hydrolysis rate of the substrate by using MALDI-TOF/MS. Alternatively, the subsite specificity of memapsin can be detd. by probing a library of inhibitors with memapsin 2 and subsequently detecting the bound memapsin 2 with an antibody raised to memapsin 2 and an alk. phosphatase conjugated secondary antibody. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the more than seventy substrate analogs were synthesized, among which MMI-005, MMI-012, MMI-017, MMI-018, MMI-025, MMI-026, MMI-037, MMI-039, MMI-040, MMI-066, MMI-070, and MMI-071 have inhibition consts. in the range of 1.4-61.4 x 109 M against recombinant pro-memapsin 2. These inhibitors are useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **271601-66-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of memapsin 2 and their use in Alzheimer's disease treatment)

RN 271601-66-2 CAPLUS

CN Octanoic acid, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12489 CAPLUS
DOCUMENT NUMBER: 134:80832
TITLE: Inhibitors of memapsin 2 and use thereof
INVENTOR(S): Tang, Jordan J. N.; Hong, Ling; Ghosh, Arun K.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; The Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000665	A2	20010104	WO 2000-US17742	20000627
WO 2001000665	A3	20010927		
WO 2001000665	C2	20020725		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1194449	A2	20020410	EP 2000-943236	20000627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003506322	T2	20030218	JP 2001-507071	20000627
US 2002049303	A1	20020425	US 2001-796264	20010228
US 2002164760	A1	20021107	US 2001-795903	20010228
US 2002115600	A1	20020822	US 2001-845226	20010430

PRIORITY APPLN. INFO.:
US 1999-141363P P 19990628
US 1999-168060P P 19991130
US 2000-177836P P 20000125
US 2000-178368P P 20000127
US 2000-210292P P 20000608
US 2000-603713 A3 20000627
US 2000-604608 A3 20000627
WO 2000-US17742 W 20000627

AB Methods for the prodn. of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been detd. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogs including isosteres at the sites of the crit. amino acid residues were developed and the substrate analogs, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition const. of OM99-2 is 1.6 x 10-9 M against recombinant pro-memapsin 2. Crystallog. of memapsin 2 bound to this inhibitor was

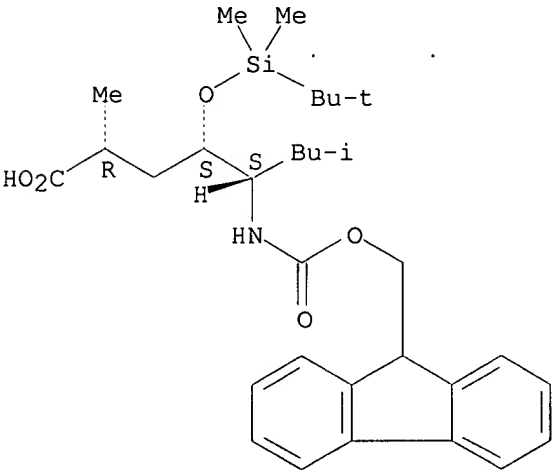
used to det. the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using com. available software programs and techniques familiar to those in org. chem. and enzymol., to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.

IT **271601-66-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors of memapsin 2 and use thereof)

RN 271601-66-2 CAPLUS

CN Octanoic acid, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:188678 CAPLUS

DOCUMENT NUMBER: 133:12663

TITLE: Design of potent inhibitors for human brain memapsin 2 (.beta.-secretase)

AUTHOR(S): Ghosh, Arun K.; Shin, Dongwoo; Downs, Debbie; Koelsch, Gerald; Lin, Xinli; Ermolieff, Jacques; Tang, Jordan

CORPORATE SOURCE: Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA

SOURCE: Journal of the American Chemical Society (2000), 122(14), 3522-3523
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

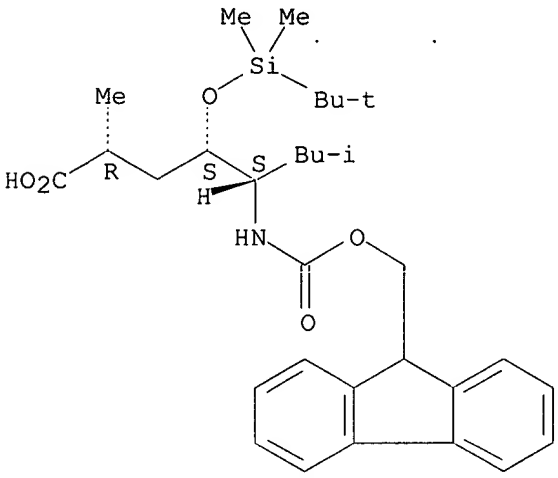
LANGUAGE: English

AB Two highly potent inhibitors of human memapsin 2 were designed and synthesized from current available specificity information. The inhibitors, OM99-1 and OM99-2, were tested for inhibition of recombinant human memapsin 2 prepd. from E. coli expression.

IT **271601-66-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and activity of potent inhibitors for human brain memapsin 2

(.beta.-secretase))
RN 271601-66-2 CAPLUS
CN Octanoic acid, 4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2,7-dimethyl-, (2R,4S,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file home
FILE 'HOME' ENTERED AT 17:45:05 ON 01 APR 2003